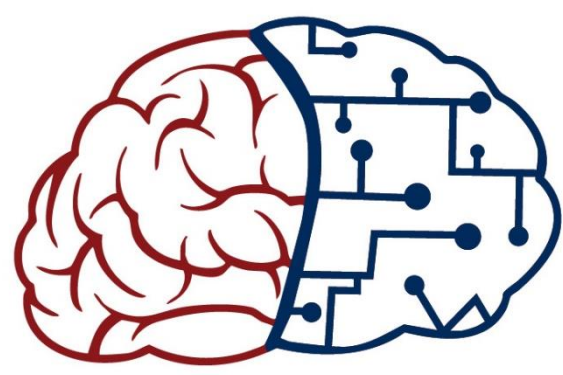




A Dual Proteomics Platform Approach To Biomarker Discovery Using Paired CSF And Plasma

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BACKGROUND

Neurodegenerative diseases require reliable biomarkers for accurate diagnosis, disease monitoring, and to facilitate clinical trials, but current tools are limited.

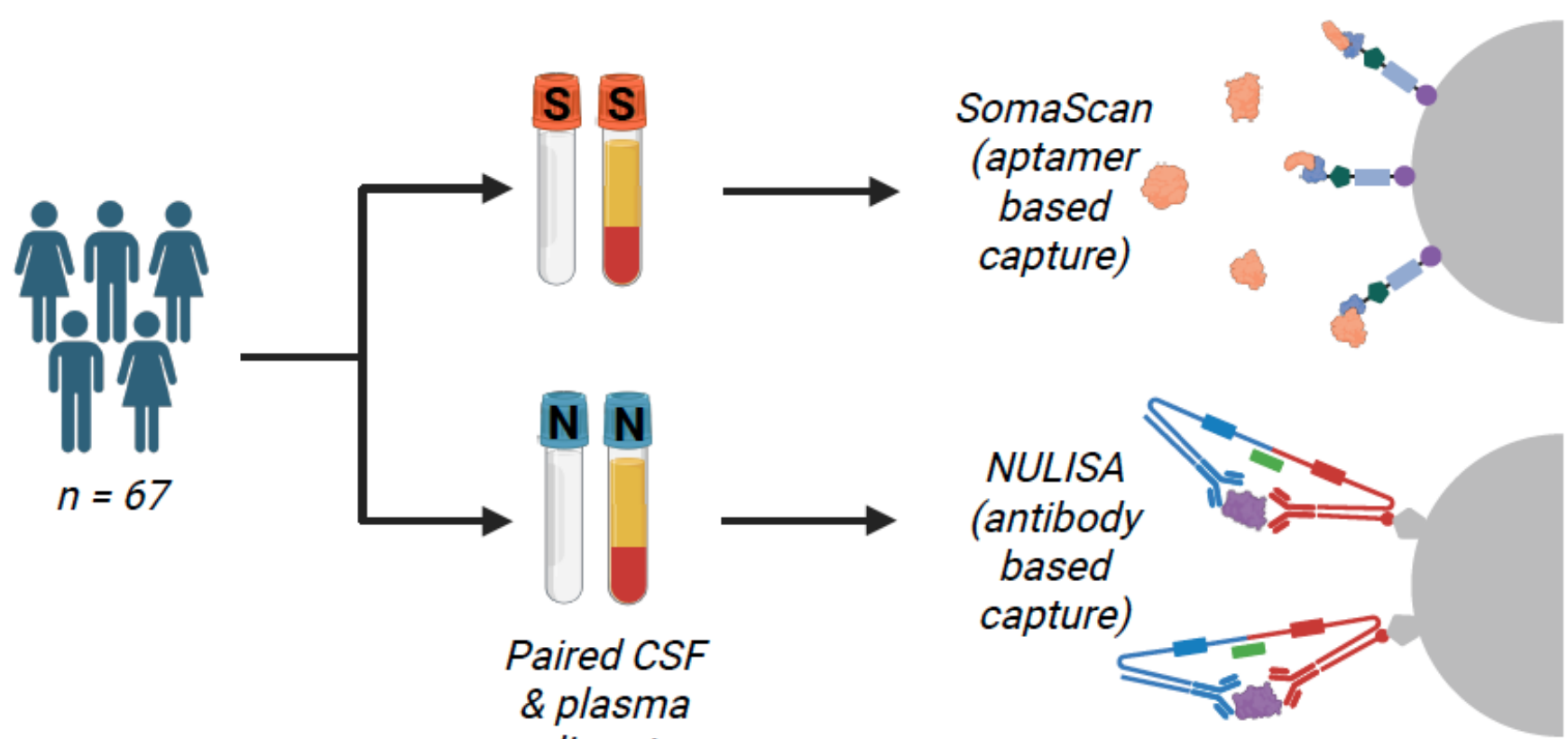
Cerebrospinal fluid (CSF) reflects central nervous system pathology more directly, but lumbar punctures are procedurally involved and considered invasive. Plasma is a more accessible and scalable source for biomarkers, but influenced by peripheral factors and may not accurately reflect brain biology. Many biomarkers show inconsistent relationships between CSF and plasma due to blood-brain barrier effects and peripheral factors, including general medical conditions.

While emerging omic technologies are an important source of discovery for candidate biomarkers, different proteomic technologies, such as aptamer-based SomaScan or antibody-based NULISA, may yield non-comparable results due to assay differences. An important step prior to validation and clinical translation of a candidate biomarker is understanding its performance in varying biofluids and assays.

Few studies systematically compare paired CSF and plasma samples across proteomic platforms, limiting the translation of biomarkers for clinical use. We aimed to perform large-scale proteomic profiling in paired CSF and plasma samples to characterize cross-compartment and cross-platform relationships.

METHODS

Study Overview



Cohort

- Participants (n=67 total; n=37 female) from the NIH Neurodegenerative Disorders Clinic (NCT03225144) with available paired CSF and plasma samples were included in this analysis
- Diagnoses included frontotemporal dementia-amyotrophic lateral sclerosis spectrum diseases, Alzheimer's disease, Lewy body disease, and presymptomatic pathogenic variant carriers
- Median age=64 (29-82; IQR 56.5-71)
- Disease severity was assessed by CDR + NACC FTLD-M Global Score

Proteomic Platforms

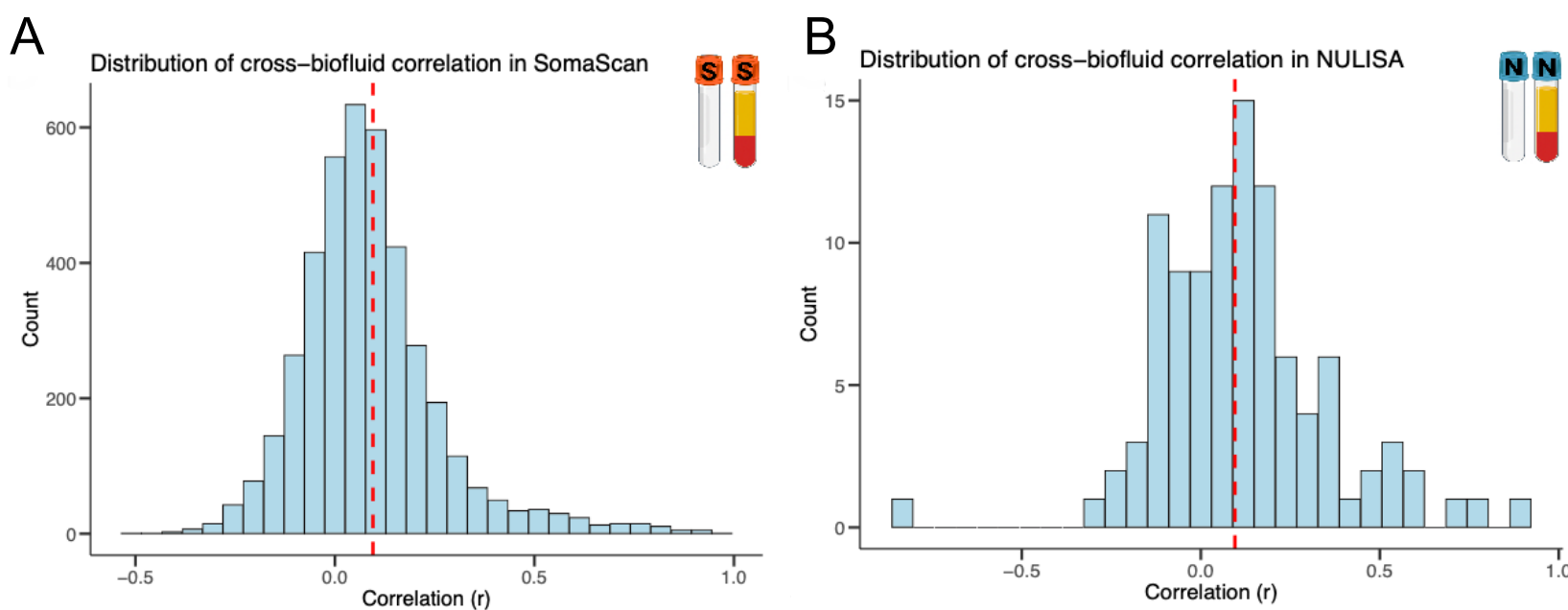
- SomaScan 11K aptamer-based, broad proteomic coverage
- NULISAseq CNS panel antibody-based targeted protein analysis

Data Analysis

- Quality filtering and normalization performed separately by biofluid
- Age and sex adjusted
- Spearman correlations for cross-biofluid (CSF vs plasma) and cross-platform (SomaScan vs NULISA) comparisons
- Multiple testing correction threshold FDR <0.05
- Exploratory regression analysis for associations with disease severity

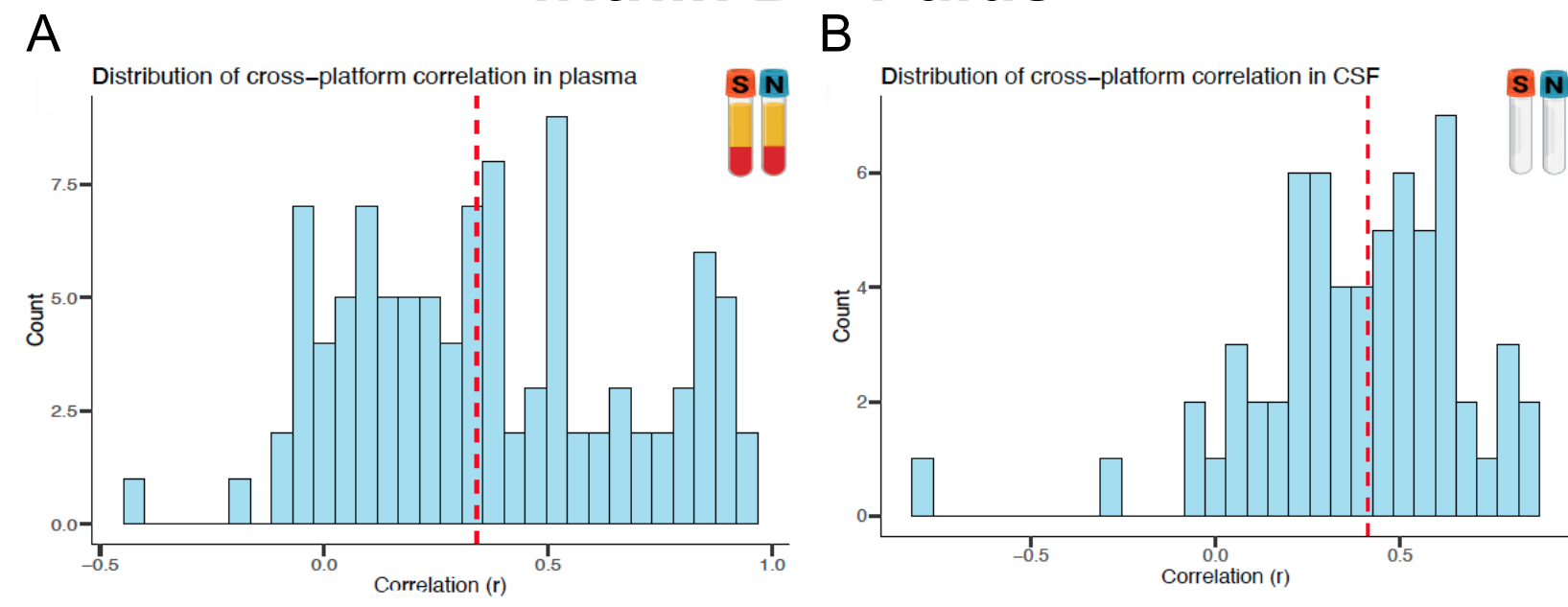
RESULTS

Cross-Biofluid Correlation is Limited



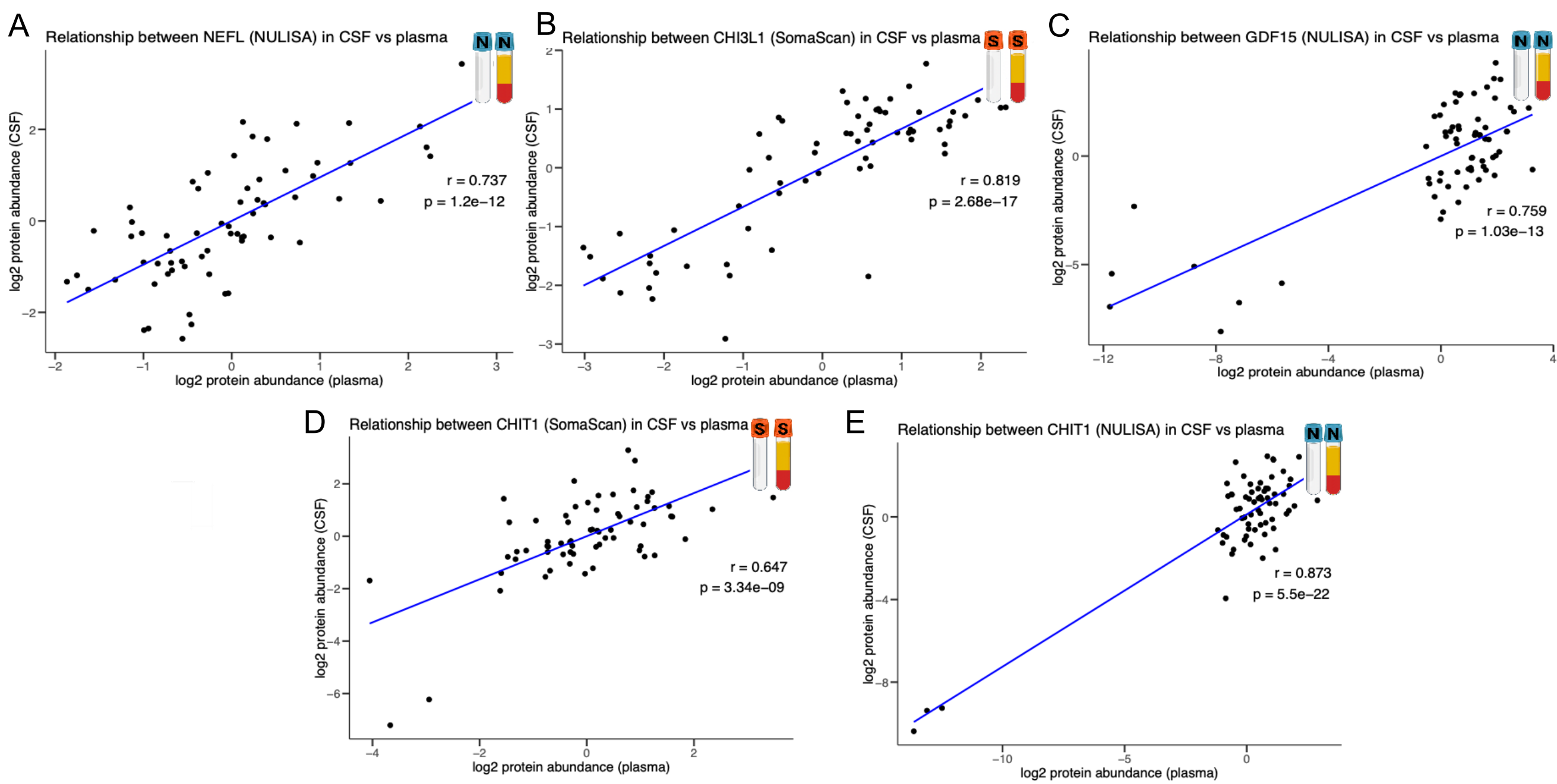
Cross-biofluid correlations were modest. **A.** SomaScan (median $\rho = 0.0664$). **B.** NULISA (median $\rho = 0.0953$).

Strong Cross-Platform Correlation within Biofluids



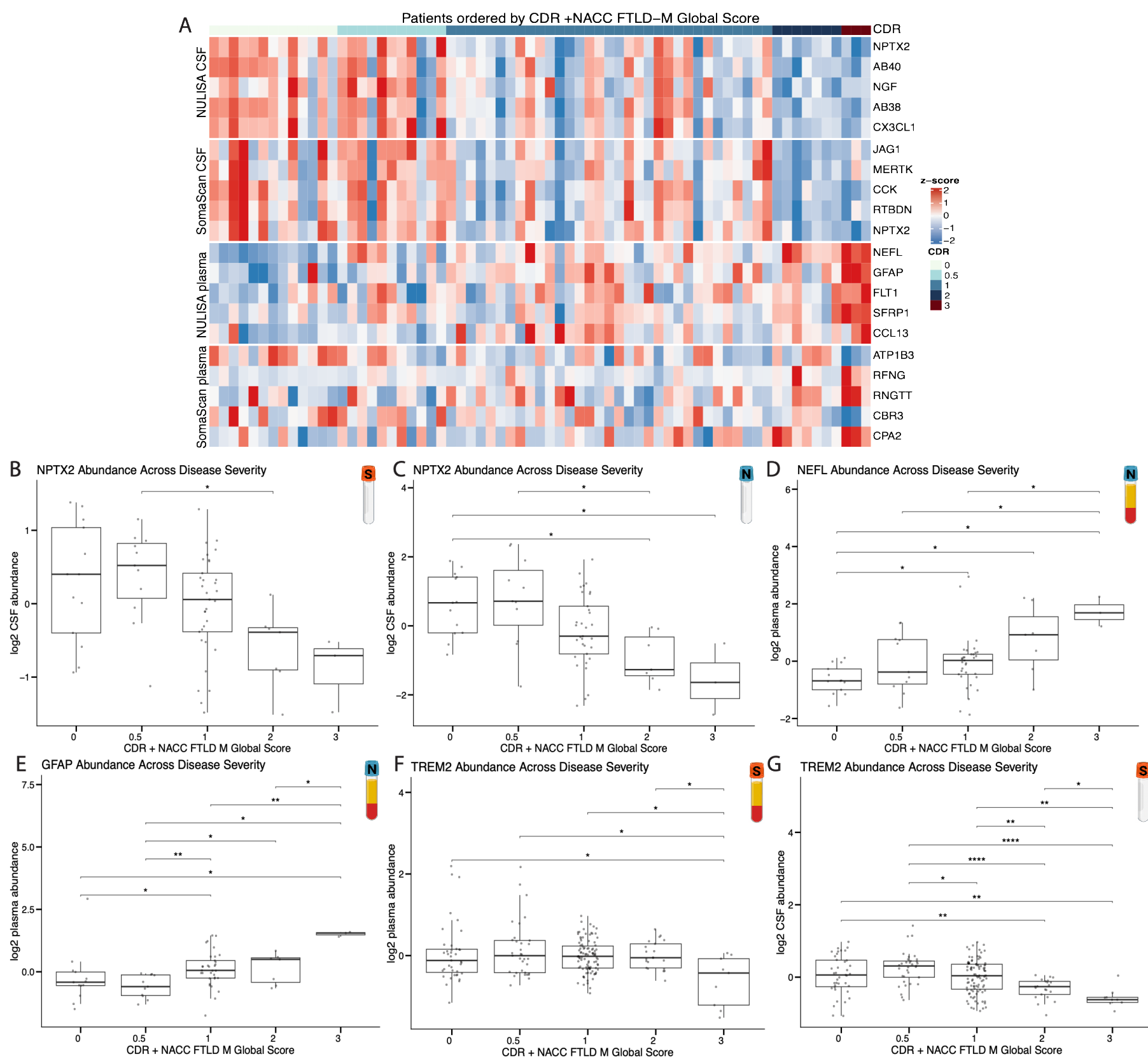
Cross-platform correlations were strong. **A.** Plasma (median $\rho = 0.341$). **B.** CSF (median $\rho = 0.421$).

Select Proteins Show Cross-Biofluid Concordance



A. Neurofilament light chain (NEFL) showed significant positive correlation across biofluids in the targeted NULISA platform ($p=0.737$, $p_{adj}=3.05E-11$) but no cross-biofluid correlation in SomaScan ($p=0.033$, $p_{adj}=0.958$). **B.** In SomaScan, Chitinase-3-like protein 1 (CHIT1, also known as YKL-40), demonstrated strong cross-biofluid correlation ($p=0.819$, $p_{adj}=5.76E-15$) but no correlation in NULISA ($p=0.180$, $p_{adj}=0.368$). **C.** In NULISA, growth differentiation factor 15 (GDF15) showed significant correlation between CSF and plasma ($p=0.759$, $p_{adj}=3.51E-12$) but no cross-biofluid correlation in the SomaScan platform ($p=0.264$, $p_{adj}=0.242$). **D and E.** In both SomaScan and NULISA, the glial marker chitinase-1 (CHIT1) was positively correlated between CSF and plasma ($p=0.647$ and 0.873 , $p_{adj}=2.16E-7$ and $5.61E-20$, respectively).

Disease Severity Associations Differ by Biofluid



A. Heatmap of top 5 proteins associated with increasing disease severity. **B and C.** NPTX2 abundance decreased significantly with increasing CDR FTLD-M global score in both SomaScan and NULISA. **D and E.** In NULISA plasma, NEFL and GFAP showed significant increases in abundance with increasing CDR score. **F and G.** TREM2, though not a top 5 predictor of disease severity (**A**), demonstrated decreasing protein abundance with increasing disease severity across biofluids in the SomaScan.

CONCLUSION

Cross-platform consistency supports biomarker robustness, while limited cross-biofluid concordance highlights compartmental biology.

We systematically compared CSF and plasma proteomic profiles in a mixed neurodegenerative disease cohort. Overall, we found strong cross-platform correlations supporting assay reliability. However, we found biofluid concordance to be limited, reflecting compartment-specific biology as well as the potential influence of systemic factors limiting translation of CSF-based biomarkers into more scalable plasma biomarkers. That said, there were several promising biomarkers with robust results, including NPTX2, TREM2, and CHIT1, which may be considered for further development. Our study has several limitations of note. First, our cohort is a relatively small clinically characterized cohort with mixed neurodegenerative diagnoses. We did not include healthy controls in this study, which are important for eventual clinical biomarker validation. This study was cross-sectional and therefore, while some markers showed correlations with disease severity, additional studies would be needed to test discriminatory performance of biomarkers in detecting disease progression. Additionally, there is only a small overlap of proteins assayed in both platforms, limiting our ability to test for additional novel markers. Both SomaScan and NULISA are not quantitative, which is another important feature of a clinically useful biomarker. In summary, biomarker performance depends both on assay and biofluid compartment and effective biomarker development requires both technical validation across platforms and an understanding of biological variation across biofluids.

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